Dkt. 06076

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Group Art Unit: 1626

JEAN LAFAY et al Examiner: R. Havlin

Serial No.: 10/582,778

Filed: August 17, 2006

For: 1-N-PHENYL-AMINO-1H-IMIDAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

DECLARATION UNDER 37 CFR 1.132

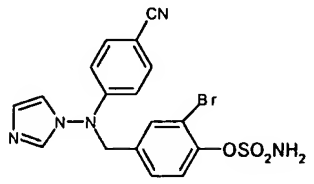
Honorable Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

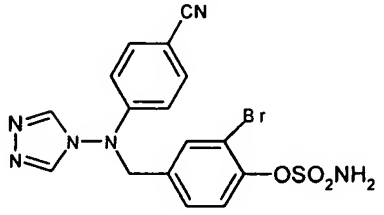
I, Jacqueline Shields, do hereby declare as follows:

I am a named inventor of the above-identified patent application.

Under my supervision, data was obtained comparing Example 45 of the present application, having the formula:



with compound B of formula:



these compounds being identical, with the exception of the imidazole group in the compound of the invention, and the triazole group in the comparative compound.

The testing of Compound B was carried out using the protocols given in the specification at pages 54-56.

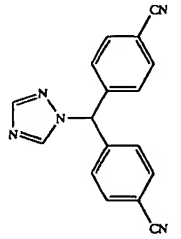
The test results for Example 45 were obtained from Table 1 of the present application.

Compound	Aromatase activity	Sulfatase activity
Example 45	IC50 (nM) = 0.13 nM	IC50 (nM) = 3.4 nM
Compound B	IC50 (nM) = 0.82 nM	IC50 (nM) = 39 nM

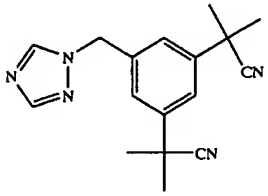
These results show that the compound of the invention has an unexpected higher aromatase activity and sulfatase activity than compound B. These results confirm that the imidazole derivatives display an increased aromatase inhibition over triazole equivalents.

The present specification includes comparative testing of numerous compounds of the invention with letrozole and anastrozole, both triazole compounds which are aromatase inhibitors used in the treatment of breast cancer.

Letrozole has the formula



while anastrozole has the formula



The data of Table 1 shows that most of the compounds tested had better aromatase inhibition activity than anastrozole, the most clinically used aromatase inhibitor in hormone-dependent breast cancer. Some of the compounds also had sulfatase inhibiting activity.

Test results using the protocols of Table 1 for other compounds according to the invention are set forth in the Table below:

	Aromatase activity		Sulfatase activity		Estrogenic potency	
Compounds	IC_{50} (nM) ± S.E.M.	n	IC_{50} (nM) ± S.E.M.	n	EC_{50} (nM) ± S.E.M	n
Ex 9	13.28± 1.91[a]	4				
Ex 10	10.57± 1.80[a]	4			nd	1
Ex 12	0.09 ± 0.01 [a]	4	--	--	nd	4
Ex 15	3.67 ± 0.8 [a]	4	--	--	nd	1
Ex 16	0.38 ±0.08 [a]	4	--	--	nd	1
Ex 42	9.96± 0.94[a]		215.3± 57.6[b]	4	Nd	1
Ex 49	4.73 ± 0.59 [c]	4	nd [c]	1	nd	1
Ex 50	50.5 ± 16.8 [c]	4	nd [c]	4	nd	1
Ex 53	36.3 ± 13 [c]	4	nd [c]	4	nd	1
Ex 55	3.5 [a]	1	nd [b]	1	nd	1
Ex 57	9 ± 3.6 [c]	4	8468 ± 430 [c]	4	nd	1
Ex 58	0.16-± 0.04 [c]	4	106 ± 42.3 [c]	5	nd	1
Ex 59	0.1 [a]	1	47.9 [b]	1	nd	1
Ex 60	31.6 [a]	1	nd [b]	1	nd	1
Ex 63	0.56 [a]	1	--	--	nd	5
Ex 67	0.78 [a]	1	--	--	nd	5

A:sulfamic acid, 3-cycloheptylmethylbenzothiophen-6-yl-1,1-dioxide-ester*
(described in WO2004/101545)
nd: not detected
Materials & methods: [a] aromatase activity alone; [b] sulfatase activity alone; [c] dual aromatase and sulfatase activity, [d] estrogenic potency.

In addition, the compounds found in Appendix A were prepared and tested, and the test results are set forth in the Table below:

	Aromatase activity		Sulfatase activity		Estrogenic potency	
Compounds	IC_{50} (nM) ± S.E.M.	n	IC_{50} (nM) ± S.E.M.	n	EC_{50} (nM) ± S.E.M	n
Ex 69	0.08 [a]	1	--	--	nd	1
Ex 71	0.03 [a]	1	--	--	nd	2
Ex 75	0.34 [a]	1	781.6[b]	1	nd	1
Ex 76	0.46 [a]	1	nd	1	nd	1

The tested compounds all had aromatase inhibition activity superior to anastrozole, and at least comparable to letrozole.

Finally, I am familiar with the references cited in the Office Action of October 15, 2009, in particular the Wermuth reference. Wermuth relates to molecular variations based on isosteric replacements and states on page 211 that *"the substitution of -CH= by -N= or -CH=CH- by -S- in aromatic rings has been one of the most successful applications of classical isoterism."*

However, after some examples, Wermuth points out that:

"In all these cases no essential activity difference is found between the original drug and its isostere. However, it can happen that the procedure fails."

Thus, one of ordinary skill in the art, given the level of unpredictability in the pharmaceutical art, would not have a reasonable expectation of success in replacing a triazole ring by an imidazole ring in a given molecule.

The Examiner also makes reference to table 13.6 on page 212, which refer to ring equivalents. In particular, Wermuth

specifies that imidazole ring would be a ring equivalent of 1,2,4-triazole (see second line of this table). However, the article of Alonso et al. (ref. 17) mentioned in table 13.6 shows that the imidazole bioisotere of ribavirin (triazole derivative) was less active or even inactive in comparison with ribavirin (see pages 836-837 the paragraph entitled "antiviral results and discussion" of Alonso reference).

Therefore, in view of Wermuth and Alonso teachings, one of ordinary skill in the art could not predict that replacing the triazole ring of Okada by an imidazole ring would result in comparable, if not substantially improved, pharmaceutical properties.

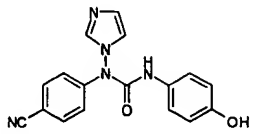
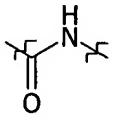
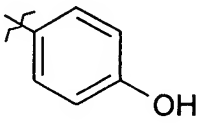
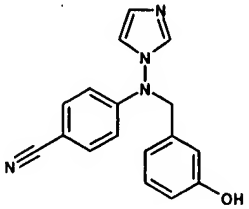
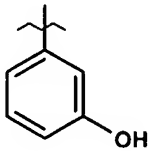
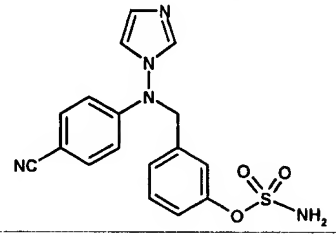
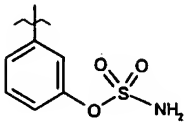
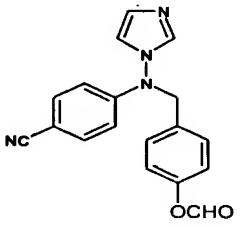
All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

15 March 2010

Date

Jacqueline Shields

Appendix A: Additional Examples

Examples	Structure	Q	Z
69			
71		CH_2	
75		CH_2	
76		CH_2